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ABSTRACT

The therapeutic efficacy of drug therapy and of psychotherapy for improving the condition of the mentally ill was examined. Results were tabulated of clinical drug trials in humans as reported in English language literature between 1954 and 1977, wherein a psychotropic drug was compared to a placebo or no treatment at all. Results of this meta-analysis indicated that there is relatively little effective difference between drug therapy and psychotherapy. Drugs plus psychotherapy proved to be the best overall treatment. Drugs were less effective for depressed patients, while the age and gender of the patient and the duration of treatment did not relate to magnitude of outcome. Better designed studies showed smaller effects than poorer designed studies. (Author/BEF)

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Comparative Effects of Drug Therapy, Psychotherapy and Drug plus Psychotherapy: A META-ANALYSIS[1]

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Drugs became a popular adjunct to milieu therapy for psychotic patients in the middle 1950's. Although the introduction met with some resistance from social psychiatrists who believed in the psychogenic nature of mental illness (Klerman, 1963), drugs rapidly made a place for themselves among the accepted treatments of psychological disorders.

In psychopharmacology quality research methods have long been the norm. Psychotropic drugs, when tested on humans, were most often examined under double blind conditions with patients randomly assigned to an active drug treatment or to an inert substance which served as a placebo. Outcome measures were varied, attrition was controlled and statistics were appropriate.

Psychopharmacologists long ago became convinced that drug therapy is effective. Undoubtedly the excellence of the research speeded the acceptance of drugs' effectiveness. Nevertheless many critics still remain among psychiatrists, psychologists and the lay public. Psychotropic drugs have been variously described as wonder medications and chemical straight jackets.

The evidence for the effectiveness of drug therapy comes from a broad ranging literature whose magnitude and speed of growth has been likened to an avalanche. Although many reviewers have tried to make sense out of major areas of the outcome literature, a broad look at the effects of drug therapy has never been attempted. Most reviewers examined the effects in human clinical trials of one drug or a genus of drugs and

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*Paper presented at the Annual Meeting of the American Educational Research Association, San Francisco, April 1979. A complete description of this research will be found in Smith, Glass and Miller. Benefits of Psychotherapy, Johns Hopkins Press, 1979.

most excluded from consideration all studies that failed to meet minimum research design, drug administration, or statistical analysis criteria, idiosyncratically defined.

In this meta-analysis canons for inclusion of research were left broad. The population of drug therapy research was defined as all clinical drug trials in humans reported in the English language literature between 1954 and 1977 wherein a psychotropic drug was compared to a placebo or to no treatment at all.[1]

Approximately 100 studies were sampled from this research domain. Their results were statistically integrated to give an estimate of the magnitude of improvement in patients who received drugs to mitigate symptoms of psychological disorders and to study the covariance with outcome of important patient and research characteristics.

The magnitude of superiority of drug therapy over a comparison condition was called the effect size. In its simplest form, the effect size was the difference between the outcome mean of the drug group and comparison group divided by the standard deviation of the comparison group. Thus effect sizes are values representing treatment success or failure in standard deviation units of treatment outcomes.

Besides answering the broad evaluation question, "How effective have drugs been in improving mentally ill patients?", the answer to another question was sought. "Among patients who are likely candidates for drug therapy, what effects can be expected when they are treated with drug therapy alone or psychotherapy alone or drug and psychotherapy in tandem?" To answer this second question an attempt was made to gather all studies in which drug therapy was compared to psychotherapy or the combination of

[1] For the reader unfamiliar with psychotropic drugs, some of the most common are by trade name: Thorazine, Stelazine, Prolixin (antipsychotics); Valium, Librium, Miltown (antianxiety agents); Tofranil, Elavil, Endep (antidepressants)

drug and psychotherapy was compared to either treatment applied separately or to a no treatment or placebo control group.

Approximately 50 such studies were gathered and their salient characteristics and results were coded. Because most studies yielded more than one outcome, about 600 outcomes were quantified for the 150 studies analyzed.

To give a flavor for the types of feature coded for each effect size and the types of research and patient sampled, some characteristics of the studies are listed in table 1.

TABLE 1: Some Characteristics of the Studies Sampled

Patient	Gender	
	Men	47%
	Women	53%
Patient	Diagnosis	
	Psychotic	37%
	Non-psychotic	48%
	Character Disorder and combination	15%
Patient	Setting	
	Inpatient	43%
	Outpatient	56%
Treatment	Drug	
	Anti-psychotic	35%
	Anti-depressant	19%
	Anti-anxiety	34%
	Other	12%
	Outcome Type	
	Hospital discharge	5%
	Somatic Symptoms	8%
	Psychological Symptoms	33%
	Adjustment	16%
	Global Mental Health	35%
	Year of Publication	
	Pre 1966	50%
	1966 to 1977	50%
	Author's Degree	
	M.D.	62%
	Ph.D.	20%
	other	18%
	Control Group Type	
	Placebo	80%
	No placebo	20%

Mean Age = 38years
Mean Treatment Duration = 3 months

The results of the 150 clinical trials represent the effects of drugs on approximately 13,000 patients.

The average patient age was 38 years. Average duration of drug therapy was about 3 months. About half the patients were men; half were women. About half were diagnosed non-psychotic (neurotic) and over a third were diagnosed psychotic. Drugs were administered about equally to inpatients and outpatients. About a third of the drugs were antipsychotics and another third were antianxiety agents; the rest, antidepressants and alcohol or drug antagonists. Most of the outcomes were measures of psychological symptoms or global health. Half the articles chosen were published since 1966. Most of the authors were medical doctors and most of the trials were placebo controlled.

In Figure 1 can be seen the drugs tested in the research and their frequency of use. Among anti-psychotic drugs chlorpromazine[1] was by far the most used. Among antianxiety agents meprobamate[2], diazepam[3] and chlordiazepoxide[4] were most popular. Imipramine[5] was the most tested antidepressant.

Many types of comparison were made in the literature. For example drugs were compared to placebo medication; drugs and psychotherapy were compared to drug therapy alone; or psychotherapy was compared to a no treatment control group. Eighteen such pair-wise comparisons were represented in the literature. These are presented in Table 2 along with the number of effect sizes derived from each type of comparison.

1 Tradename - Thorazine
2 Tradename - Equinol or Miltown
3 Tradename - Valium
4 Tradename - Librium
5 Tradename - Tofranil

Figure 1

Frequencies of Psychotropic Drugs in Studies Sampled

ANTIPSYCHOTIC DRUGS	FREQUENCY
Acetophenazine	1
Chlorpromazine	27
Fluphenazine	3
Haloperidol	3
Insulin	2
Lithium	4
Loxapine	2
Mepazine	1
Penfluridol	1
Perphenazine	3
Pimozide	2
Prochlorperizine	1
Promazine	1
Promethazine	1
Thioridazine	4
Thiothixene	4
Trifluoperazine	10
Triflupromazine	2
Reserpine	9

ANTIANXIETY DRUGS	
Benactyzine-Meprobamate	2
Cartazolate	1
Chlorazepate Dipotassium	1
Chlordiazepoxide	11
Diazepam	12
Hydroxyzine	1
Listica	1
Lorazepam	2
Meprobamate	14
Oxazepam	1
Phenobarbital	6
Prazepam	1
Propanolol	2
Ripazepam	1

Figure 1 (Continued)

ANTIDEPRESSANT DRUGS	FREQUENCY
Amitriptyline	8
Benactyzine	1
Dextroamphetamine	2
Doxepin	1
Imipramine	15
Iprindole	1
Iproniazid	3
Isocarboxazid	2
Isoniazid	1
Methylphenidate	1
Nialamide	1
Opipramol	1
Phenelzine	5
Protriptyline	1

OTHERS	
ACTH	1
Amitriptyline-perphenazine	2
Chlormethiazole	1
Chlorpromazine-procyclidine	1
Chlormezanone	1
Disulfiram	1
L-5 Hydroxytryptophan	1
LSD	2
Metronidazole	2
Naloxone	1
Penicillamine	1
Thiopropazate-dihydrochloride	2
Tranylcypromine-Trifluoperazine	1

These 60 drugs appeard 197 times in 152 studies

*Some studies used more than one drug so the total exceeds 152, the number of studies sampled. Frequencies are by studies, not effect sizes.

Table 2: ABOUT THE COMPARISONS

Type of Comparison			Number of Effect Sizes	Percent of Effect Sizes
Drug Only	vs.	Placebo	323	55%
Drug Plus Psychotherapy	vs.	Placebo	19	3
Psychotherapy	vs.	Placebo	6	1
Psychotherapy Plus Placebo	vs.	Placebo	13	2
Drug	vs.	Psychotherapy	6	1
Drug Plus Psychotherapy	vs.	Psychotherapy	26	4
Psychotherapy Plus Placebo	vs.	Psychotherapy	6	1
Drug	vs.	Psychotherapy Plus Placebo	1	
Drug Plus Psychotherapy	vs.	Psychotherapy Plus Placebo	69	12
Drug	vs.	Regular Treatment Minus Drug	21	4
Drug Plus Psychotherapy	vs.	Regular Treatment Minus Drug	18	3
Psychotherapy	vs.	Regular Treatment Minus Drug	15	3
Drug	vs.	No Treatment or Placebo	20	3
Drug Plus Psychotherapy	vs.	No Treatment or Placebo	8	1
Psychotherapy	vs.	No Treatment or Placebo	11	2
Psychotherapy Plus Placebo	vs.	No Treatment or Placebo	6	1
Placebo	vs.	No Treatment or Placebo	11	2
Drug Plus Psychotherapy	vs.	Drug	10	2

Taken together the comparisons provided information about the independent effects of drug therapy and psychotherapy and their effects when combined. A simple schematization of the comparisons is represented in Figure 2. The comparisons are arranged to provide a first approximation of the effects of the three types of intervention.

Figure 2: Factorial Display of 565 Effect Sizes

Psychotherapy

No Drug Therapy

$\overline{ES}$=.323 S_x=.56

Comparison	$\overline{ES}$	S_x	n
P v O	.598	.451	11
P v pl	.257	.221	6
D+P v D	.412	.709	10
P+pl v pl	.411	.411	13
P v Reg	.111	.634	15
P+pl v O	.132	.173	6
*D v P	.485	-	6
*D v P+pl	-.525	-	1

N=68

Drug Therapy

$\overline{ES}$=.650 S_x=.57

Comparison	$\overline{ES}$	S_x	n
D+P v O	.919	.371	8
D+P v pl	.361	.411	19
D+P v Reg	.836	.434	18

N=45

No Psychotherapy

n=0

Drug Therapy

$\overline{ES}$=.492 S_x=.73

Comparison	$\overline{ES}$	S_x	n
D v O	.583	.419	20
D v pl	.493	.721	310
D v Reg	.610	.384	21
D+P v P	.008	.826	26
D+P v P+pl	.610	.309	68
*D v P	.335	-	6
*D v P+pl	1.35	-	1

N=452

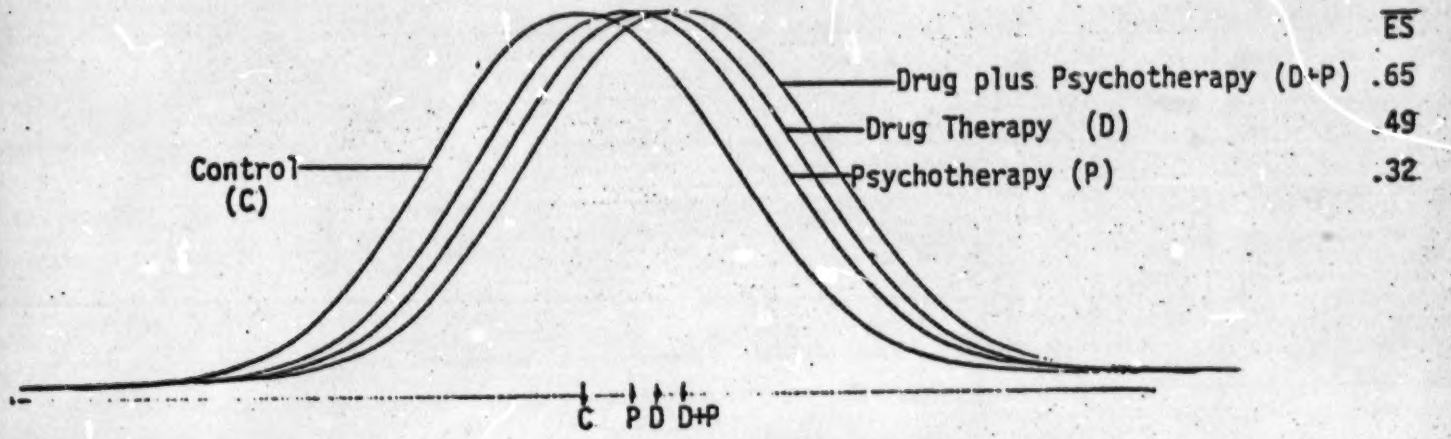
*Control Referenced Effect Size (for explanation see Smith, Glass and Miller, 1979).

D=drug only O=nothing P=psychotherapy only pl=placebo Reg=regular treatment minus drug

D+P=drug plus psychotherapy P+pl=psychotherapy plus placebo

These results are displayed as overlapping normal curves in Figure 3.

Figure 3: Relative Effects of Drug Therapy, Psychotherapy, and Drug Plus Psychotherapy



The average psychotherapy patient lies at the 63%ile of the untreated group
The average drug treated patient lies at the 70%ile of the untreated group
The average drug plus psychotherapy patient lies at the 74%ile of the untreated group.

Drug plus psychotherapy shows a $.65s_x$ effect, drug therapy alone shows a $.49s_x$ effect and psychotherapy alone a $.32s_x$ effect.

Each treatment is superior to control. Whereas the average untreated patient lies at the 50th percentile of his own group, the average psychotherapy patient lies at the 63rd percentile of the untreated group. The average drug treated patient lies at the 70th percentile of the untreated group and the average drug and psychotherapy treated patient lies at the 74th percentile of the untreated group.

One should be cautious in comparing the psychotherapy or the drugtherapy effect found here with the one reported in the meta-analysis of Smith and Glass (1977). In the work of those authors psychotherapy was conducted on a

less disturbed patient population. The average age of the patients in the Smith-Glass psychotherapy meta-analysis was about 23 years; in this literature the average age for patients receiving psychotherapy was 37 years. Fifty percent of these patients were diagnosed psychotic but only 7 percent of the Smith-Glass patients were psychotic. Almost half of these patients were institutionalized, but under a fifth of the patients in the Smith-Glass literature were inpatients.

The results from this intial analysis do not control for extraneous differences between the three therapies represented in the 2x2 table in Figure 2. Differences in types of patient treated, types of outcome measured and types of patient setting, for example, could contribute to differences in observed effects that one wishes to attribute to therapeutic differences alone.

An important subset of data help to improve the comparisons between therapies by reducing confounding variable. These are data from experiments in which combinations of the three therapies were directly compared to one another or simultaneously compared to a control group. In these experiments types of outcome, patient characteristics, settings in which therapy is administered, etc. are held constant. In Table 2 are shown results of these same-experiment data. They confirm the results of the original analysis.

The far right column shows the average difference in effectiveness of the three therapies. Drug plus psychotherapy shows a .18 standard deviation superiority to drug therapy alone. The superiority of drug therapy to psychotherapy is shown in the same-study analysis to be about .19 standard deviations. Finally, drug plus psychotherapy is shown to be .29 standard deviations superior to psychotherapy. All are very close approximations to the earlier data.

Table 1.2 Effect Sizes from Experiments in which Therapies were Directly Compared or Simultaneously Compared to a Control

Treatment 1 and 2 Compared to Control in Same Study				Treatment 1 and 2 Directly Compared in Same Study				Estimated Difference Between Treatments 1 and 2 Directly Compared or Compared to Control in Same Study[1]
(1)				(2)				(3)				(4)
Drug Only (D)				Drug+Psychotherapy (D+P)				D vs. D+P				D vs. D+P
ES	N[2]	S_{ES}	$S_{\overline{ES}}$	ES	N	S_{ES}	$S_{\overline{ES}}$	ES	N	S_{ES}	$S_{\overline{ES}}$	ES
.496	49	.413	.059	.65	45	.571	.085	.278	15	.627	.168	$.18s_x$ favoring Drug + Psychotherapy
N studies = 15				N studies = 8								N studies = 23
Drug Only (D)				Psychotherapy Only (P)				D vs. P				D vs. P
ES	N	S_{ES}	$S_{\overline{ES}}$	ES	N	S_{ES}	$S_{\overline{ES}}$	ES	N	S_{ES}	$S_{\overline{ES}}$	ES
.832	37	.42	.069	.306	32	.55	.098	.02	8	.82	.29	$.19s_x$ favoring Drug Therapy
N studies = 10				N studies = 6								N studies = 16
Drug+Psychotherapy				Psychotherapy Only				D+P vs. P				D+P vs. P
ES	N	S_{ES}	$S_{\overline{ES}}$	ES	N	S_{ES}	$S_{\overline{ES}}$	ES	N	S_{ES}	$S_{\overline{ES}}$	ES
.653	27	.488	.09	.173	25	.516	.103	.20	27	.943	.093	$.29s_x$ favoring Drug +Psychotherapy
N studies = 7				N studies = 9								N studies = 16
Drug+Psychotherapy				Psychother.+placebo				D+P vs. P+pl				D+P vs. P+pl
ES	N	S_{ES}	$S_{\overline{ES}}$	ES	N	S_{ES}	$S_{\overline{ES}}$	ES	N	S_{ES}	$S_{\overline{ES}}$	ES
.417	23	.377	.079	.323	19	.395	.091	.58	78	.809	.093	$.47s_x$ favoring Drug +Psychotherapy
N studies = 8				N studies = 26								N studies = 34

Results from 7 studies in which drug therapy, psychotherapy, and drug plus psychotherapy were compared to a control

Drug Only				Psychotherapy Only				Drug plus Psychotherapy			
ES	N	S_{ES}	$S_{\overline{ES}}$	ES	N	S_{ES}	$S_{\overline{ES}}$	ES	N	S_{ES}	$S_{\overline{ES}}$
.50	25	.41	.08	.173	25	.516	.103	.65	27	.488	.094

[1]This column represents the weighted mean (by number of comparisons) of the mean difference between column 1 and 2 with the treatment difference in column 3. The number of comparisons attached to the mean difference between col. 1 and 2 is the mean number of comparisons for col. 1 and 2. So D vs. D+P in col. 4 = $.18s_x$ because .65-.496=((.154)(47)+.278(15))/62

[2]Number of comparisons/effect sizes

in Miller, Thomas I . "Comparative effects of drug therapy, psychotherapy, and drug plus psychotherapy: a meta-analysis."

Having reported the comparative effects determined by this analysis it must yet be noted that a more comprehensive complex and correct analysis was undertaken in which all the above comparisons were used but the information was treated in a different way.[1] In this analysis each comparison between pairs

[1] Thanks are due to Gene Glass who conceived of the problem in this unique way and solved it. A complete description of this technique is reported in Smith, Glass & Miller, Benefits of Psychotherapy, Johns Hopkins Press, to be published 1979.

of treatment or treatment and control was treated as one element in a system of linear equations which were used to simultaneously estimate three unknown parameters;the drug therapy effect, the psychotherapy effect, and the interaction effect. Use of standard least squares estimation for the same-experiment data yielded essentially the same results as reported earlier:

Drug effect = .44
Psychotherapy effect = .32
Drug plus psychotherapy = .61

Uhlenhuth (1960, p. 60) offered 4 possible models for the interaction of drug therapy and psychotherapy.

> "1. Addition, the effect of the two interventions combined equals the sum of their individual effects. 2. Potentiation, the effect of two interventions combined is greater than the sum of their individual effects. 3. Inhibition, the effect of two interventions combined is less than the sum of their individual effects. 4. Reciprocation, the effect of two interventions combined equals the individual effects of the more potent intervention."

Data from the same-experiment subset seem to support best the Inhibition model. There is no support in any analysis for models of potentiation or reciprocation. Least squares estimation using all the data, not just the same-experiment subset, has suggested an additive model of interaction, but because fewer confounding variables are controlled in those data, results from that analysis are considered less reliable.

Results Classified by Characteristics of Patients and Research Quality.

Effect size is broken into six major categories in Table 3. In the drug only literature non-psychotic patients appear more improved than psychotic patients.

Table 3

Effect Sizes for Patient Major Diagnosis

Type of Patient	Drug Only $\overline{ES}$	Drug Only s_{ES}	Drug Only N	Drug-Plus-Psychotherapy $\overline{ES}$	Drug-Plus-Psychotherapy s_{ES}	Drug-Plus-Psychotherapy N
Psychotic	.493	.434	130	.802	.645	29
Non-Psychotic	.623	.885	159	.374	.233	16
Mixed (including character disorder)	.221	.470	70			0
Totals	.498	.686	359	.650	.571	45

This trend is reversed in the drug plus psychotherapy research. When the outcomes of placebo controlled studies were weighted equally with the results of studies using no placebo, the superiority of drug plus psychotherapy for psychotic patients still obtains but drug therapy affects psychotic and non-psychotic patients about equally. (See Table 4)

Table 4:Effect sizes for equal weighting of placebo and untreated control comparisons

Patient Diagnosis	Average Effect Sizes: Drug Therapy	Average Effect Sizes: Drug-Plus-Psychotherapy
Psychotic	$\overline{ES}_{.} = .55$	$\overline{ES}_{.} = .69$
Non-Psychotic	$\overline{ES}_{.} = .60$	$\overline{ES}_{.} = .39$

In Table 5 are shown average effects for specific patient diagnosis. The superiority of drugs for anxious patients compared to depressed patients clearly can be seen in this table.

Table 5

Effect Sizes for Specific Diagnosis

Type of Patient	Drug Only			Drug-Plus-Psychotherapy		
	$\overline{ES}$	s_{ES}	N	$\overline{ES}$	s_{ES}	N
Schizophrenic	.495	.550	108	.802	.645	29
Depressive	.367	.698	85	.460	.160	7
Anxious	.663	.950	87	.370	.232	4
Other (including character disorder and other)	.410	.650	43	.565	.064	2
Total	.495	.689	323	.693	.566	42

In Table 6 are shown effect size values for degree of blinding in experiments and type of assignment of patients to treatments. It can be seen that single or double blinded research produced smaller drug effects than non-blinded research. Random assignment of patients to treatment and control was associated with smaller effects than effects from matched or intact group experiments.

In Table 7 are shown correlations with effect size of some continuous variables. Only the percent of black patients being treated correlated reliably with effect size over all drug and drug plus psychotherapy studies. More black patients were associated with smaller drug therapy effects.

Table 6

Average Effect Sizes for Degrees of Blinding and Methods of Patient Assignment to Treatments

Degree of Blinding	$\overline{ES}$.	s_{ES}	N
None or "Open"	.62	.51	74
Single (patient or assessor blind)	.50	.44	50
Double (patient and assessor blind)	.49	.75	271
Assignment of Patients to Treatments	$\overline{ES}$.	s_{ES}	N
Random	.48	.65	334
Matching	.54	.51	16
Intact Groups (non-random)	.72	.88	45

Table 7

Correlations of Selected Characteristics with Effect Size

Characteristic	Drug Therapy		Drug-Plus-Psychotherapy		Total	
	Correlation, r	N	Correlation, r	N	Correlation, r	N
Year of Publication	-.01	358	-.42**	45	-.05	403
Age	.04	324	-.24	43	.00	367
Percent Male	-.07	310	.16	43	-.04	353
Percent White	.06	77	-.09	19	.05	96
Percent Black	-.29*	35	-.31	12	-.30*	47
Duration of Treatment	.02	356	-.04	45	.03	401
Months after therapy that effects were measured	-.03	357	.19	45	.02	402

*$p < .05$

**$p < .01$

Conclusion: Relatively little difference in therapeutic efficacy obtained between drug therapy and psychotherapy. Drug plus psychotherapy was the best treatment overall. Drugs were less effective for depressed patients but age of patient, patient gender, and duration of treatment surprisingly did not relate to magnitude of outcome. Better designed studies showed smaller effects than poorer designed studies.

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Notes

[1] All data reported herein obtained from two major sources:

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